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IMBALANCE OF THE REDOX STATE IN OPA GENE RELATED DISORDERS: MATHEMATICAL APPROACHES TO DEFINE PATHOGENESIS

Aurelie Millet[1], Nadege Merabet[1], Baptiste Alric[1], Marlene Daloyau[1], Pascal Reynier[2], Anne Galinier[3], Anne Devin[4], Bernd Wissinger[5], Pascale Belenguer[1], Joel Bordeneuve-Guibe[6] and Noelie Davezac[1]

[1]CBD-UMR 5547, Universite Toulouse III, Toulouse, France
[2]U694 INSERM, CRNH Angers, UFR Sciences medicales, Angers
[3]STROMALAB, CHU Toulouse-Hôpital de Rangueil, Toulouse, France
[4] IBGC du CNRS, 1 rue Camille Saint Saëns, Bordeaux Cedex, France
[5]University of Tübingen, Germany
[6] ISAE SUPAERO, Universite de Toulouse, Toulouse, France

OPA1 mutations cause Dominant Optic Atrophy (DOA), an incurable retinopathy with variable severity and which mechanisms are still unknown. More than 20% of patients will endure a DOA plus syndrome with ataxia, deafness or Parkinsonism. We evidenced oxidative stress in a mouse model of the pathology and aimed to identify the consequences of OPA1 inactivation on redox homeostasis. We monitored the levels of mitochondrial respiration, reactive oxygen species (ROS), anti-oxidant defences and cell death by biochemical and *in situ* approaches using in vitro and in vivo models of OPA1 related disorders. Increased ROS levels were observed in cortices of the murine model OPA1$^{+/-}$ as well as in OPA1 down-regulated cortical neurons. This increase is associated to a decline in mitochondrial respiration and an increase of antioxidant enzyme levels. Upon exogenous oxidative stress OPA1-depleted neurons did not further up-regulated antioxidant defenses. Finally, low levels of antioxidant enzymes were observed in fibroblasts from patients supporting their role as modifier factors. Our study shows: (i) the pro-oxidative state induced by OPA1 loss can be considered as a pathological mechanism (ii) differences in antioxidant defences can contribute to the variability in expressivity and (iii) antioxidant defences can be used as prognostic tools to gauge the severity and the evolution of the disease. Furthermore, our discovery offers a way to model mathematically the dysfunctions of oxidative metabolism in OPA1 gene related disorders. We will present the last results of our algorithm and wet laboratories experiments.

noelie.davezac@univ-tlse3.fr